The present invention, as defined broadly in Claim 1, is directed to a method of expressing a therapeutic agent in a human. The method comprises administering autologous $CD34^+$ cells obtained from cord blood to the human. The autologous $CD34^+$ cells have been genetically engineered to include at least one nucleic acid sequence encoding a therapeutic agent.

Applicants are the first ones to demonstrate that one can obtain $CD34^+$ cells from cord blood of a patient, genetically engineer such $CD34^+$ cells to include at least one nucleic acid sequence encoding a therapeutic agent, and return such genetically engineered $CD34^+$ cells of the circulatory system of the patient, whereby the genetically engineered $CD34^+$ cells express the therapeutic agent in vivo. Such has been demonstrated in Example 2 of the specification. Although the prior art discloses the genetic engineering of $CD34^+$ cells, such prior art at best provides sheer speculation that one may obtain $CD34^+$ cells from cord blood, genetically engineer such $CD34^+$ cells obtained from cord blood, and administer such genetically engineered $CD34^+$ cells to a patient.

Anderson discloses the transduction of T-cells with the adenosine deaminase gene. The transduced T-cells then were given to human patients in order to treat severe combined immune deficiency. Although Anderson discloses the possibility of transducing an enriched population of $CD34^+$ cells, Anderson does not disclose or even remotely suggest to one of ordinary skill in the art that $CD34^+$ cells may be obtained from cord blood and transduced with a nucleic acid sequence encoding a therapeutic agent, whereby such transduced cells are administered to a patient in order to express the therapeutic agent in the patient.

Moritz discloses the transfection of cord blood cells with retroviral vectors including the neomycin resistance gene or the adenosine deaminase gene. Moritz, however, provides no suggestion to one of ordinary skill in the art that $CD34^+$ cells may be separated from other cord

blood cells prior to the transduction of the cells, or that genetically engineered $CD34^+$ cells may be administered to a human patient in order to achieve expression of a protein in the patient.

Kohn discloses culturing $CD34^+$ cells obtained from bone marrow in the presence of Interleukin-1, Interleukin-3, Interleukin-6, and human mast cell growth factor to provide for improved retroviral transduction of such cells. Kohn, which is directed solely to obtaining $CD34^+$ cells from bone marrow; does not disclose or even remotely suggest to one of ordinary skill in the art that one can obtain $CD34^+$ cells from cord blood, transduce such $CD34^+$ cells with a nucleic acid sequence encoding a therapeutic agent, and administer the transduced $CD34^+$ cells to a human patient in order to express the therapeutic protein in the patient.

Boyse discloses isolating human neonatal or fetal blood components containing hematopoietic stem cells, introducing a heterologous gene sequence into the stem cells, whereby the gene sequence is incorporated stably into the stem cells, and capable of being expressed by the progeny of the stem cells. Boyse, however, does not disclose or suggest to one of ordinary skill in the art that one can obtain $CD34^+$ cells from the cord blood of a patient, genetically engineer the $CD34^+$ cells with at least one nucleic acid sequence encoding a therapeutic agent, and administer the autologous $CD34^+$ cells in order to express the therapeutic agent in the patient.

Moore discloses the isolation of $CD34^+$ cells from cord blood followed by the expansion of such $CD34^+$ cells <u>in vitro</u> in the presence of cytokines. The expanded $CD34^+$ cells then are transduced with a retroviral vector including a mutated dehydrofolate resistance gene. Moore, however, does not disclose or even remotely suggest to one of ordinary skill in the art that one may obtain $CD34^+$ cells from the cord blood of a patient, genetically engineer such $CD34^+$ cells with at least one nucleic acid sequence encoding a therapeutic agent, and administer the

genetically engineered $CD34^+$ cells to a patient in order to express the therapeutic agent in the patient.

Applicants are the first to provide a method of expressing a therapeutic agent in a human by administering autologous $CD34^+$ cells obtained from cord blood to the human, wherein the autologous $CD34^+$ cells have been genetically engineered to include at least one nucleic acid sequence encoding a therapeutic agent. The cited prior art, when taken in combination, at best provides sheer speculation that such a method as claimed by Applicants could be effected. Because the cited prior art contains nothing more than sheer speculation that Applicants claimed method could be effected, the cited prior art does not render Applicants' claimed method obvious to one of ordinary skill in the art. It is therefore respectfully requested that the rejection under 35 U.S.C. 103 be reconsidered and withdrawn.

Claims 1-5 stand rejected under 35 U.S.C. 112, first paragraph, because the specification does not reasonably provide enablement for the treatment of any and all diseases with any and all nucleic acids. This rejection is respectfully traversed.

The Examiner admits that the specification is enabling with respect to the administration of autologous $CD34^+$ cells obtained from cord blood and which include the adenosine deaminase gene. Although, as the Examiner states in the Office Action, the Kohn 1995 paper may indicate further work is required with respect to other genes, such statement in the Kohn 1995 paper does not mean that other genes may not be transduced successfully into autologous $CD34^+$ cells obtained from cord blood or that such genetically engineered $CD34^+$ cells could not be administered to a human in order to express a therapeutic agent in the human. Because Applicants have demonstrated that the method of the present invention may be employed to express the ADA gene in a human, one skilled in the art would expect reasonably that autologous

$CD34^+$ cells obtained from cord blood could be engineered with nucleic acid sequences other than the ADA gene, and that such nucleic acid sequences would be expressed in a human upon administration of the genetically engineered $CD34^+$ cells to the human. The Examiner has provided no evidence, other than speculative statements, which would indicate to one skilled in the art that proteins other than ADA could not be expressed in accordance with the claimed method. Thus, the Examiner cannot assert that the claimed method is not enabling for nucleic acid sequences other than the ADA gene. For the above reasons and others, the specification provides an enabling disclosure, and it is therefore respectfully requested that the rejection under 35 U.S.C. 112 first paragraph, be reconsidered and withdrawn.

For the above reasons and others, this application is in condition for allowance, and it is therefore respectfully requested that the rejections be reconsidered and withdrawn and a favorable action is hereby solicited.

Respectfully submitted,

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Date of Signature